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TO: Examiner Freistein

COMPANY: USPTO

FAX NO.: 1-571-273-8300

FROM: Kevin D. McCarthy

RE: 10/512,024 (0-06-224 (16120/US/03))

DATE: 1/26/2007

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Typed Name: Kevin D. McCarthy
Date: January 26, 2007

Patent 0-06-224/16120/US/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Haj-Yehia, Abdullah I.
Serial no.: 10/512,024
I.A. Filed: April 15, 2003
Title: BETA-AGONIST COMPOUNDS COMPRISING NITRIC OXIDE DONOR GROUPS AND REACTIVE OXYGEN SPECIES SCAVENGER GROUPS AND THEIR USE IN THE TREATMENT OF RESPIRATORY DISORDERS
Examiner: Andrew Freistein
Art Unit: 1626

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir/Madam:

Response and Amendment

This response is in reply to the office action mailed on September 28, 2006. This response is being submitted with a petition for a three-month extension to time to submit the response, with a corresponding Form 2038.

In this response, we address the claim amendments, the restriction requirement and election of claims. For the record, the current claims are claims 1-28 as presented when the application was nationalized on October 19, 2004, and as set forth in the communication submitted on December 15, 2004, not claims 1-38 as set forth in the office action. Accordingly, the amendments are in accordance to the current claims of 1 to 28.

Claim amendments

1. The set of claims is being amended as shown on the attached marked-up pages, deleting claims 10 and 11, and amending claims 1, 3, 4, 8, 9, 12, 14, 27, and 28.

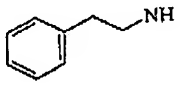
   Amending claims 1, 8, 9, and 12, and canceling claims 10-11 address the Examiner's restriction requirement, and, while

traversing said requirement, the applicant presently elects the matter incorporated essentially in Group II (or partially in Groups I-III, as explained below). Formula I has been, without prejudice, limited to cases when R^1 is - SNO, R^3 with R^4 form a saturated heterocycle, and R^5 is H or alkyl.

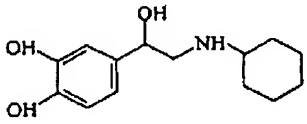
The dependency amendments in claims 3, 4, 12, 27, and 28 are believed to still more emphasize unity of the invention.

Election/Restrictions

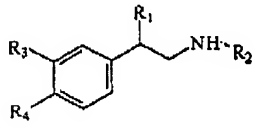
2. The Examiner combined various features of the invention into Groups I to XX, noting that his grouping is only exemplary because a precise grouping cannot be made (page 3 of his letter); and further, he suggests that the structural moiety common to Groups I to XX is



(page 8 of the Examiner's letter). The Examiner then cites Johansson et al. who disclose the following structure



(KWD 2314, Table 1). The Examiner concludes that said moiety common to Groups I to XX fails to define a contribution over the prior art, implying that the publication comprises the claimed fragment. The Examiner may have in mind formula of instant claim 1

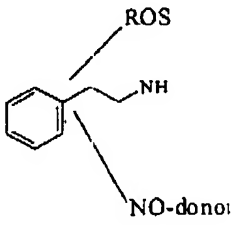


in which R1, R3 and R4 are OH, and R2 is cyclohexyl. The applicant wishes to respectfully demonstrate that the Examiner's conclusions

may have resulted from disregarding an essential factor of the invention.

The Examiner's kind attention is directed to the principal feature of the claimed compounds, as reflected in the title of the invention, and as defined in claim 1, the principle feature being the presence of at least one ROS scavenger and at least one NO-donor group in the molecule.

3. The above said essential feature is totally absent in the cited publication. It is not surprising that the compounds of the invention and the cited compounds have an overlapping moiety – both are β-agonists. But the instant compounds comprise beside a β-agonist moiety additional features which make them, as a person skilled in the art may appreciate, totally different from the known compounds. Each of the additional features of the instant compounds distinguishes them from the prior compounds, let alone their combination: the novel compounds of the invention release NO, a strong signal transducer, in the site of action, and furthermore, they neutralize deleterious ROS-radicals. The structural moiety common to Groups I to XX, as suggested by the Examiner should be, therefore, amended as follows



obtaining a structure that obviously cannot overlap with any of the prior art formulae.

4. In view of the above explanation, the applicants believe that the Examiner will detract the restriction requirement, at least at its current broad wording. However, in order to comply with the requirement, only a part of the invention features are now elected, with traverse, as explained below.

Amended claim 1, restricted with traverse, now includes only structures in which R^1 is –SNO; in which R^3 with R^4 together form substituted 5 to 7-membered saturated heterocycle having 1 or 2 heteroatoms; and in which R^5 is –H or alkyl. It is believed that these

conditions essentially fall within the Examiner's feature selection under his "Group II", in which R^1 is SNO, R^3 and R^4 form an isoindole together with the phenyl ring, and R^5 is H or alkyl. It is respectfully submitted that amended claim 1 may have other features, possibly complying with the feature definition of Examiner's "Group I" to "Group III", but since the Examiner's selections are, according to his own advice, mainly exemplary, it is believed that the applicant's current election complies with the spirit of the Examiner's feature grouping; if, however, the applicant is wrong, the Examiner is respectfully requested to call the undersigned attorney for clarifying the matter.

Inventiveness (non-obviousness) of the instant invention

5. The Examiner implies that the instant invention would be obvious over the cited prior art, stating that claims 1-38 are not so linked as to form a single inventive concept. Since the essential feature, as explained in paragraph 2 above, comprises combining three pharmaceutically important features in one molecules, namely β-agonist activity with NO donating activity and with ROS-scavenging activity, mainly for use in treating respiratory diseases, and since that feature has not been even distantly hinted in the cited document, the feature would not have been obvious.

6. Furthermore, the novel compounds, claimed in the instant application, not only comprise active groups absent in the cited prior art, but they have biological activities that are superior to the activities of prior materials. For example, the IC_{50} of instant compound 2 is lower than 10^{-10} (instant Fig. 1), while the published materials had IC_{50} greater than 10^{-9} , wherein the mentioned KWD 2314 had IC_{50} even much greater than 10^{-7} (Table 2 in the publication).

Conclusions

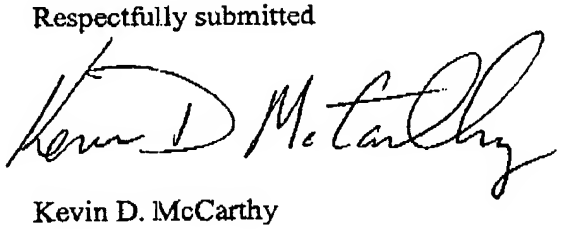
7. The claims of the instant application relate to a clearly defined group of compounds, being substituted aminoethyl benzenes, wherein among the substituents there is at least one NO-donor selected from four structures (ONO, ONO_2, SNO, NONOate), and at least one ROS-scavenger selected from four structures (nitroxide, alkenyl, sulfhydryl, aryl); a process for preparing the compounds, and their use are further included. Aminoethyl benzenes of the prior art do not comprise either NO-donor or ROS-scavenger, let alone both. In response to a restriction requirement, the claims have been

restricted to a fraction of original compounds, which are believed to be novel and inventive; and claim 1 is now believed to be novel and inventive, as well as all other claims, that now depend from claim 1, and cover a process and a use of said novel compounds. The amended claims are now belied to be allowable.

8. Since the Examiner's Summary did not take into consideration the feature that is believed by applicants as essential, it is respectfully requested that the restriction requirement be kindly reconsidered. It is believed that the excluded compounds also comprise novel and inventive, useful, materials.

It is respectfully submitted that this application is currently in a condition for allowance and such allowance is earnestly solicited.

Respectfully submitted



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